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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/484,886	SMITH ET AL.	
	Examiner	Art Unit	
	Kailash C. Srivastava	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *132-152* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *132-152* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Response and amendment filed 16 December 2009 to the Office Action mailed 22 June 2009 is acknowledged and entered.

Claims Status

2. Claims 1-131 have currently been cancelled.

3. Claims 132-152 have currently been added.

4. Claims 132-152 are currently pending and are examined on merits.

Withdrawals In View of Arguments

5. In view of remarks and amendments filed 16 December 2009 in response to the Office Action mailed 22 June 2009 and interview in person conducted on 15 December 2009 with Applicants' Representatives and Ms. Manon Cox, the following objections and Rejections in the Office Action mailed 22 June 2009 are hereby withdrawn:

- Objection to Claims 96-116 and 127-131 for lack of metes and bounds of Claims 96-98 and 127-131 and improper dependency of Claims 97-116; and

- Anticipatory rejection of Claims 96-97, 99-116 and 130 as unpatentable under 35 U.S.C. §102(b) as anticipated by Quelle et al. (Blood. 1989. Volume 74, Pgs. 652-657) with evidence provided by Dorland's Illustrated Medical Dictionary (W. B. Saunders Co., Philadelphia, 1988, Page 581).

Rejoinder

6. In consideration of remarks and amendments filed 16 December 2009 and to harmonize the newly presented product claims with the method (i.e., process) claims and further according to the provisions under 37 C.F.R. §1.41 Groups I-III encompassing Claims 43-89 and 91-95 previously withdrawn from consideration as a result of a restriction requirement in Office Action mailed 17 October 2002 (See Pages 3-4, items 6- 7), are now subject to being rejoined and are hereby rejoined (See, M.P.E.P., §821.04). Accordingly, the **Restriction Requirement in Office action mailed on 17 October 2002 is hereby withdrawn** and all the claims (i.e., 43-95 now cancelled but re-presented as Claims 132-152) presented in this application are fully examined for patentability.

Objection to Claims – Minor Informalities

7. In view of amendments filed 16 December 2009, newly presented Claims 132-152 objected to because of the following informalities:

- As currently worded, Claim 132 at line 6 does not describe, "serum-free cultured insect cells". Are the insect cells serum-free or said cells are cultured in a culture medium that is free of serum?

- Each of Claims 151-152 are objected to because at Line one of each one of Claims 151-152, before the word "wherein" a --, -- should be inserted. Appropriate correction is required.

All other claims depend directly from the objected Claim 132 and are, therefore, also objected for the reasons set forth.

Double Patenting

8 The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Long*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R. 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

9. Claims 132 and 151-152 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-11 of U.S. Patent 6,103,536 A to Smith et al. Although, the conflicting claims are not identical, they are not patentably distinct from each other because said claims in said Patent point to same product having same distinguishable properties expressed and produced in same insect cells transfected with baculovirus expression system comprising a recombinant baculovirus. Claims 8-11 of 6,103, 526 A describe a recombinant erythropoietin having an activity of about 200,000 U/mg protein to about 500,000 U/mg protein (See Claims 10-11), wherein said

erythropoietin is produced in *Spodoptera frugiperda* Sf900+ ATCC CRL-12579 cells transfected with baculovirus expression system (Claim 1, Line 1) comprising a recombinant baculovirus (Claim 8, Lines 2-3 and Claim 9). Thus, one of skill in the art would have been able to apply the teachings of Smith et al. from the US Patent 6,103, 526 A to expect successful results for the instantly claimed product by process invention and would have been motivated to claim method based on the claimed subject matter in the U.S. Patent cited *supra.*

Claim Rejections - 35 U.S.C. §112

35 U.S.C. 112, first Paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> ***The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.***

Scope Enablement

11. Newly presented Claims 133-138 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for:

- a method and apparatus for culturing and monitoring different cultivation parameters for culturing a cell line in a variety of bioreactors (e.g., dialysis reactor, loop reactors, stirred tank reactors);
- a method to culture and monitor parameters for insect cell culture transfected with an expression vector to express and produce an expression product;
- applicability of said expressed and produced product in said bioreactors; and
- high cell density growth of Sf 900+ insect cells to express and produce an expression product of baculovirus expression system;

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with said claims describing an erythropoietin (i.e., EPO) having an *in vitro* activity of at least 200,000 U/mg protein and 500,000 U/mg protein (Specification Pages 1-54 and Pages 1-4 of supplemental specification filed 12/17/2002) because in said

specification there is no description for *in vitro* activity for said EPO. Thus, the "Essential claimed subject matter" that of EPO having an *in vitro* activity of any dimension or *in vitro* activity is missing in the specification.

From the record of the present written disclosure as pointed out *supra*, the scope of the claimed invention recited in claims 133-138 is not supported by the specification on record because in said specification there is no mention of an erythropoietin having an "*in vitro* activity" that is claimed in the newly presented Claims 133-138. Thus, in the absence of reciting the critical elements, i.e., the *in vitro* activity of said erythropoietin; the specification is not commensurate in scope with those claims.

A person of skill would not be able to practice the invention because undue experimentation will be required to obtain an erythropoietin having an *in vitro* activity of the quantities mentioned in the specification without the type of activity (i.e., *in vitro* or *in vivo*).

Undue experimentation will be required due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as illustrated below.

A. Quantity of Necessary Experimentation

The specification evidences "a substantially pure, recombinant erythropoietin (i.e., rEPO) that is glycosylated, produced by a baculovirus expression system, is purified to $\geq$ 95%, has relative homogeneity, stimulates erythropoiesis (amendment to Specification filed 12/17/2002, Page 3, lines 15 and 26-29) and in a great detail elaborates the bioreactors, the process parameters/ control of said parameters to cultivate cells, especially insect cells including Sf900+ cells. Said specification, however, does not evidence an erythropoietin, or a rEPO having erythropoietin (i.e., EPO) having an *in vitro* activity of at least 200,000 U/mg protein and 500,000 U/mg protein (Specification Pages 1-54 and Pages 1-4 of supplemental specification filed 12/17/2002) because in said specification there is no description for *in vitro* activity for said EPO., or how said activity was evaluated (See Specification Pages 1-54 and amendment to Specification filed 12/17/2002, Pages 2-4).

Thus, a person of skill will have to perform a number of permutations and combinations to practice the claimed composition of instant invention.

B. Limited Amount of Guidance

The specification, or the amended specification filed 12/17/2002, as currently presented; does not provide a clear-cut guidance for an erythropoietin (EPO) having *in vitro* activity because said EPO having an "in vitro activity" of the quantities mentioned in the specification are not described in said specification or the amendment to said specification.

C. Limited Number of Working Examples in the Specification

In the specification, or the amended specification filed 12/17/2002, as currently presented, the description only describes an EPO having "an activity of at least 200,000 U/mg (indeed about 500,000 U/mg)" and does not evidence said EPO having an *in vitro* activity of > 500,000 U/mg protein, (Specification Pages 1-54 and Pages 1-4 of supplemental specification filed 12/17/2002.

D. Nature of the Invention

The currently presented specification in view of the Declarations of Ms. Manon Cox filed respectively on 03/24/2004 and 03/24/2005 only delineates the claimed EPO having an activity of at least 200,000 U/mg protein and 500,000 U/mg protein, but not an activity of > 500,000 U/mg protein because said specification, or the amended specification filed 12/17/2002, do not describe said EPO having any other in *vitro* activity.

E. State of the Prior Art

The prior art description in the specification is adequate regarding the EPO, rEPO and properties of an EPO or rEPO according to the summarized description prevalent in the pertinent art.

F. Relative Skill Level of those in the Art

At least a Bachelor Degree in Biochemical engineering, Biochemistry, Biology, Biomedical engineering, Biophysics, Chemistry, Cytology, Enzymology, Microbiology, Molecular biology, Pharmacology, or Proteomics.

G. Predictability or Unpredictability in the Art

Unless supported with illustrative experimental evidence, biological materials/ responses/ phenomenon are unpredictable. Thus, information obtained under one set of detrimental parameters may not be extrapolated for another set of materials/ parameters/products or specific conditions.

H. Breadth of the Claims

As noted above, in item A, the claim limitations (e.g., in *vitro* activity) are unspecified/un-illustrated or not defined in the corresponding specification of the instant application. Thus, the claimed invention is drawn upon claims that are not supported by the presently detailed specification.

New Matter

12. Newly presented Claims 133-138 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Within Pages 1-54 of the specification as filed on 18 January 2000, or the amended specification filed 12/17/2002, as currently presented, the specification fails to recite a "substantially pure, recombinant glycosylated erythropoietin, produced by a baculovirus expression system in cultured insect cells, wherein said erythropoietin has an "*in vitro* activity of > 500,000 U/mg protein, or at least 500,000 U/mg protein". This is because in said specification the description is of EPO having an activity, not an EPO having an *in vitro* activity of any particular quantification.

From the record of the presently filed written disclosure, the specification does not teach adequate support for the claimed EPO having an in *vitro* activity as claimed. Furthermore, new matter can't be added in an amendment.

35 U.S.C. 112, Second Paragraph

13. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> ***The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.***

14. Claims 132-152 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- The phrase "relative homogeneity" at Claim 132, line 8 renders said Claim incomprehensible, unclear and vague and therefore indefinite. Said phrase does not describe the reference point

for said "relative homogeneity". To what said homogeneity is being related to? Accordingly, the metes and bounds for said, "relative homogeneity" are not described. Appropriate correction/clarification is required.

- The phrase "varies from high value to low value over about 10 to 30 minutes or over about 20 minutes" at Claim 149 Lines 3-4 renders said Claim incomprehensible, unclear and vague and therefore indefinite. The word "about" in and by itself means "in vicinity of" whereas the phrase "10 to 30 minutes or over about 20 minutes" gives the range along with the variation in the claimed number, or in vicinity of which claimed number or parameter should be present. Thus, this is a range in range situation, one range given according to the recitation, "about" and the other according to the phrase, "10 to 30 minutes or over about 20 minutes". A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). Appropriate correction is solicited.

All other rejected claims depend directly from the rejected Claim 132 and are, therefore, also rejected for the reasons set forth above.

Claim Rejections - 35 U.S.C. §103(a)

15. The following is a quotation of 35 U.S.C. §103(a) that forms the basis for all obviousness rejections set forth in this Office action:

> ***A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having***

ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § *103*(c) and potential 35 U.S.C. § *102*(f) or (g) prior art under 35 U.S.C. § 103(a).

17. Newly presented Claims 132-138 and 151 are rejected under 35 U.S.C. §103(a) as obvious over Quelle et al. (Blood. 1989. Volume 74, Pgs. 652-657) in view of Dorland's Illustrated Medical Dictionary (W.B. Saunders Co., Philadelphia, 1988, Page 581) and further in view of Inlow et al. (1989. INSECT CELL CULTURE AND BACULOVIRUS PROPAGATION IN PROTEIN-FREE MEDIUM. Journal of Tissue Culture Methods, Volume 12, Number 1, Pages 13-16).

Claims 132-138 and 151 are drawn to a "substantially pure, recombinant. glycosylated erythropoietin (EPO) produced by a baculovirus expression system in serum-free cultured insect cells, said insect cells are *Spodoptera frugiperda* cells, wherein said EPO is purified to 95% or greater, has relative homogeneity, *in vivo* activity and stimulating erythropoiesis" and said EPO has an *in vitro* activity of at least 200,000 U/mg protein, or > 200,000 U/mg protein, or between 200,000 U/mg protein and 500,000 U/mg protein, or 500,000 U/mg protein, or > 500,000 U/mg protein, or at least 500,000 U/mg protein.

Regarding newly presented Claims 132-138 and 151, Quelle et al. teach a glycosylated, > 99% pure, recombinant human erythropoietin produced by a baculovirus expression system, said expression system cultured in an insect cell, wherein said erythropoietin has an activity of 200,000 U/mg protein (Page 652, Column 1, Lines 6-25 and Column 2, Lines 6-13). Quelle et al., also teach that said insect cells are *Spodoptera frugiperda*, Sf9, cells (Page 652, Abstract, Line 6) and said activity of said EPO was tested *in vivo* in ex-hypoxic, polycythemic mice (Page 653, Column 1, Lines 6-8 under Table 1). Please note that erythropoiesis is an inherent activity of erythropoietin (See Dorland's Illustrated Medical Dictionary, Page 581, Column 1, Lines 38-41). Furthermore, the advantages of further purifying a partially-purified protein/hormone, for which receptors have been recognized and for which a use is known, provide sufficient reason to find the purified protein/hormone to have been obvious to one of ordinary skill at the time of the invention. Some of the advantages of the purification being, that purified protein/hormone: are more storage-stable; generally exhibit an increased specific activity; are amenable to

amino acid sequencing which can lead to recombinant means of protein/hormone production with its accompanying savings in costs; and, allow for ready separation of reaction products as compared to separations which must account for impurities. These advantages are well known to the artisan of ordinary skill. Such knowledge may provide the suggestion to modify the explicit teachings of the relied upon reference or to combine references. See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 297 n.24, 227 USPQ 657, 667 n.24 (Fed. Cir. 1985). Examiner's position is that well known purification techniques would be employed with a reasonable expectation of success in providing a purified product possessing the claimed properties. Thus, an "obvious to try" standard is not being applied herein. See *In re O'Farrell*, 853 F.2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). From above discussion it is clear that, Quelle et al teach a similar product prepared in the same manner and having same range of activity (i.e., 200,000 U/mg to 500,000 U/mg) as claimed in the instantly claimed invention. Therefore, the product would intrinsically function in the same, or essentially the same manner as in the instantly claimed invention. Instantly claimed higher purity of said erythropoietin is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter, which is well within the purview of the skilled artisan. Therefore, the product disclosed in the prior at reference would intrinsically stimulate erythropoiesis even with "little *in vivo* activity". Quelle et al. however, are silent regarding growing said *Spodoptera frugiperda* cells in a serum-free culture medium.

Inlow et al. teach preparing (Page 14, Column 2, Line 36 to Page 15, Column 1, Line 10) a serum-free medium (ISFM) to grow *Spodoptera frugiperda* Sf9 cells and further teach that in the ISFM, final densities reached in the presence or absence of serum to 4-6 x 10^6/ml (Page 15, Column 2, Lines 29-39, especially, Lines 36-39 and Figure 1). Additionally, the levels of recombinant proteins produced by the Sf9-baculovirus expression system cultured in the ISFM is same in the presence or absence of serum (Page 16, Lines 5-8 below Figure 1).

The instantly claimed invention is a product-by-process. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. According to M.P.E.P. §2113, "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (Citations omitted). In instant invention, the claimed erythropoietin product is clearly documented in the

cited prior art.

One having ordinary skill in the art at the time of instantly claimed invention would have been motivated to modify the teachings from Quelle et al. according to the teachings generally known in the art and from Inlow et al. to obtain an EPO from insect cells cultured in a serum-free medium, wherein said EPO is substantially pure, recombinant. glycosylated, has an *in vitro* activity of at least 200,000 U/mg protein, or > 200,000 U/mg protein, or between 200,000 U/mg protein and 500,000 U/mg protein, or 500,000 U/mg protein, or > 500,000 U/mg protein, or at least 500,000 U/mg protein because; as discussed in preceding paragraph methods to purify a protein/hormone and advantages of having a purified protein/hormone are well documented in the art and Inlow et al. teach a serum free culture medium to cultivate the Sf9 insect cells to produce the baculovirus expression vector system-mediated recombinant protein.

Thus, at the time of instantly claimed invention was made it would have been *prima facie* obvious to one of ordinary skill in the art to modify teachings from Quelle et al. according to the teachings generally known in the art and from Inlow et al., to obtain an EPO from insect cells cultured in a serum-free medium, wherein said EPO is substantially pure, recombinant. glycosylated, has an *in vitro* activity of at least 200,000 U/mg protein, or > 200,000 U/mg protein, or between 200,000 U/mg protein and 500,000 U/mg protein, or 500,000 U/mg protein, or > 500,000 U/mg protein, or at least 500,000 U/mg protein ; because techniques to purify proteins are generally known in the art and it is also generally known in the art that the functional efficiency and rheological properties (e.g., shelf life) of said purified protein/hormone increases and because Inlow et al., teach a serum free culture medium to cultivate the Sf9 insect cells to produce the baculovirus expression vector system-mediated recombinant protein.

From the teachings of the reference cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. Newly presented Claims 139-150 are rejected under 35 U.S.C. §103 (a) as obvious over combined teachings from Quelle et al. (Blood. 1989. Volume 74, Pgs. 652-657) in view of Dorland's Illustrated Medical Dictionary (W.B. Saunders Co., Philadelphia, 1988, Page 581) and Inlow et al. (1989. INSECT CELL CULTURE AND BACULOVIRUS PROPAGATION IN PROTEIN-FREE MEDIUM.

Journal of Tissue Culture Methods, Volume 12, Number 1, Pages 13-16) as applied to Claims 132-138 and 151 and further in view of Morrison (US Patent 5,002,890).

Newly presented Claims 139-150 additionally recite a method of producing EPO of Claim 132 by culturing insect cells in at least one bioreactor, supplying culture medium to said bioreactor vessel for culture medium, a liquid medium circulation loop designed to circulate a cell free medium, a semi-permeable membrane, dissolved oxygen control and a dialysis feed subsystem in addition to a means for releasing dissolving oxygen.

Regarding newly presented Claims 139-150, teachings from Quelle et al. in combination with teachings from each of Dorland's Illustrated Medical Dictionary and Inlow et al. have been discussed in item 14 *supra.* Quelle et al. are silent regarding a bioreactor having a liquid medium circulation loop designed to circulate a cell free medium, a semi-permeable membrane, dissolved oxygen control and a dialysis feed subsystem in addition to a means for releasing dissolved oxygen.

Morrison teaches a bioreactor to support cell growth for cell culture, wherein said bioreactor includes a vessel for culture medium, a liquid medium, a liquid medium circulation loop designed to circulate a cell free medium, a semi-permeable membrane, oxygenator; dialysis feed subsystem in addition to a means for releasing dissolving oxygen. Morrison additionally teaches a gas exchange system with a semi permeable membrane that provides for transport of oxygen through the systems main loop. Morrison's system provides a feedback control microprocessor that is capable of measuring, chemical parameters, pH, carbon dioxide, concentration of dissolved oxygen, of the cell culture system (Column 6, line 5 to Column 8, line 12). Morrison is silent regarding the means for delivery of oxygen being outside of the bioreactor. However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide a means for delivery of oxygen outside of the bioreactor, since it has been held that rearranging parts of an invention involves only routine skill in the art (See, *In re Japikse*, 86, USPQ 70).

One having ordinary skill in the art at the time of the claimed invention would have been motivated to modify/combine the teachings from Quelle et al. according to the teachings generally known in the art, teachings from Inlow et al. and Morrison to obtain an EPO as discussed in item 14; because methods to purify a protein/hormone and advantages of having a purified protein/hormone are well documented in the art, Inlow et al. teach a serum free culture medium to cultivate the Sf9 insect cells to produce the baculovirus expression vector system-mediated recombinant protein and Morrison teaches a bioreactor having a liquid medium circulation loop designed to circulate a cell free medium, a semi-

permeable membrane, dissolved oxygen control and a dialysis feed subsystem in addition to a means for releasing dissolved oxygen.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify/combine the teachings from Quelle et al. according to the teachings generally known in the art to purify a protein/hormone and advantages of purification; Inlow et al., and further in view of Morrison because general methods for purifying a protein are well documented in the pertinent prior art; Inlow et al., teach a serum free culture medium to cultivate the Sf9 insect cells to produce the baculovirus expression vector system-mediated recombinant protein and Morrison teaches a bioreactor having a liquid medium circulation loop designed to circulate a cell free medium, a semi-permeable membrane, dissolved oxygen control and a dialysis feed subsystem in addition to a means for releasing dissolved oxygen.

`From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Newly presented Claim 152 is rejected under 35 U.S.C. §103 (a) as obvious over combined teachings from Quelle et al. (Blood. 1989. Volume 74, Pgs. 652-657) in view of Dorland's Illustrated Medical Dictionary (W.B. Saunders Co., Philadelphia, 1988, Page 581) and Inlow et al. (1989. INSECT CELL CULTURE AND BACULOVIRUS PROPAGATION IN PROTEIN-FREE MEDIUM. Journal of Tissue Culture Methods, Volume 12, Number 1, Pages 13-16) in view of Morrison (US Patent 5,002,890) as applied to Claims 132-151 and further and additionally *en Arguendo* in view of Smith et al (U.S. Patent 6, 103,526 A).

Newly presented Claim 152 additionally recites, wherein the insect cells are *Sporodoptera frugiperda* SF900+ cells.

Regarding newly presented Claims 139-151, teachings from Quelle et al., in combination with teachings from each of Dorland's Illustrated Medical Dictionary, Inlow et al., and Morrison have been discussed in items 18-19 *supra.* Quelle et al., while discussing production of said EPO in *Sporodoptera frugiperda* SF9 cells are, however, silent regarding production of said EPO in *Sporodoptera frugiperda* SF900+ cells.

Smith et al. teach a recombinant erythropoietin having an activity of about 200,000 U/mg protein to about 500,000 U/mg protein (See Claims 10-11), wherein said erythropoietin is produced in *Spodoptera frugiperda* Sf900+ ATCC CRL-12579 cells transfected with baculovirus expression system (Claim 1, Line 1) comprising a recombinant baculovirus (Claim 8, Lines 2-3 and Claim 9).

One having ordinary skill in the art at the time of the claimed invention would have been motivated to modify/combine the teachings from Quelle et al. according to the teachings generally known in the art, teachings from Inlow et al., Morrison, and Smith et al. to obtain an EPO as discussed in item 18; because methods to purify a protein/hormone and advantages of having a purified protein/hormone are well documented in the art, Inlow et al. teach a serum free culture medium to cultivate the Sf9 insect cells to produce the baculovirus expression vector system-mediated recombinant protein, Morrison teaches a bioreactor having a liquid medium circulation loop designed to circulate a cell free medium, a semi-permeable membrane, dissolved oxygen control and a dialysis feed subsystem in addition to a means for releasing dissolving oxygen and Smith et al. teach producing a recombinant erythropoietin having an activity of about 200,000 U/mg protein to about 500,000 U/mg protein, wherein said erythropoietin is produced in *Spodoptera frugiperda* Sf900+ ATCC CRL-12579 cells transfected with baculovirus expression system comprising a recombinant baculovirus.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to modify/combine the teachings from Quelle et al. according to the teachings generally known in the art to purify a protein/hormone and advantages of purification; Inlow et al., Morrison, and Smith et al., because general methods for purifying a protein are well documented in the pertinent prior art; Inlow et al., teach a serum free culture medium to cultivate the Sf9 insect cells to produce the baculovirus expression vector system-mediated recombinant protein, Morrison teaches a bioreactor having a liquid medium circulation loop designed to circulate a cell free medium, a semi-permeable membrane, dissolved oxygen control and a dialysis feed subsystem in addition to a means for releasing dissolving oxygen and Smith et al teach an rEPO produced in *Spodoptera frugiperda* Sf900+ cells, wherein said EPO has an activity of about 200,000 U/mg protein to about 500,000 U/mg protein. Furthermore, it is also *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." (*In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted)). In the instant case, the two compositions being said EPO and said *Spodoptera frugiperda* Sf900+ insect cells, wherein said insect cells produce said EPO as instantly claimed.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. For reasons aforementioned, no Claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at (571)-272-0925 Monday through Thursday 7:30 A.M. to 6:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system,

contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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10 March 2010

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